Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Could SARS-CoV-2 cause tauopathy?

A large cohort study on the neurological sequelae of COVID-19 found that approximately 34% of patients received a psychiatric or neurological diagnosis within 6 months of SARS-CoV-2 infection.[1] Some of these diagnoses are indicative of acute or subacute changes to the CNS. Although the long-term consequences of these changes are unknown, viral infection in a subset of patients might promote chronic neuroinflammation and, over a period of years, lead to tau aggregation and neurodegeneration.

Tauopathies are characterised by the deposition of insoluble aggregated tau in neurons and, occasionally, glial cells. Tauopathies are classified as either primary, in which tau is thought to be the driver of disease, or secondary, in which tau aggregation is downstream of another insult. Secondary tauopathies can have a wide range of causes, from extracellular accumulation of amyloid β to repetitive head trauma. Although the exact mechanism for how these diverse insults lead to tau aggregation and neurodegeneration is still poorly understood, secondary tauopathies are associated with neuroinflammation. In particular, activation of the NLRP3 inflammasome can promote tau hyperphosphorylation and the formation of neurofibrillary tangles.[2] The activation of the NLRP3 inflammasome, triggered during SARS-CoV-2 infection, could lead to downstream tau aggregation and neurodegeneration.

SARS-CoV-2 might cross the blood–brain barrier and directly infect neurons or the surrounding vasculature, as shown in non-human primates.[3] Once inside cells, SARS-CoV-2 can directly activate the NLRP3 inflammasome[2] and induce tau mislocalisation[4] in human cells in vitro.

A second possible mechanism by which SARS-CoV-2 could affect the CNS is through inducing a widespread systemic inflammatory response. For example, cytokines released in systemic inflammation can activate glial cells. The increase in cytokine levels during SARS-CoV-2 infection, including interleukin (IL)-18 and IL-1β, can also lead to activation of the NLRP3 inflammasome.[2] Activation of NLRP3 by these cytokines has been observed in the brain in murine models.

Accumulated exposures to pathogens that contribute to neuroinflammation might increase the risk of developing a tauopathy. For example, the subacute sclerosing panencephalitis and postencephalitic parkinsonism tauopathies have been suggested to be triggered by viral infections. These diseases share the neuropathological hallmarks of hyperphosphorylated tau, neurofibrillary tangles, and neurodegeneration.[5] In post-mortem samples from individuals with subacute sclerosing panencephalitis, measles virus has been detected in neurons and glial cells that contain tau neurofibrillary tangles.[5] Postencephalitic parkinsonism is thought to be a long-term sequela of encephalitis lethargica that occurred during and after the 1918 influenza pandemic. Subacute sclerosing panencephalitis is diagnosed 3–34 years (median 9–10 years) after measles infection, whereas postencephalitic parkinsonism was generally diagnosed 1–5 years after encephalitis lethargica.[6]

Only 0·01–0·1% of measles infections lead to subacute sclerosing panencephalitis.[5] If a COVID-19-induced tauopathy develops at a similar rate, there could be 10 000–100 000 cases for every 100 million people infected with SARS-CoV-2. However, the proportion of individuals infected with SARS-CoV-2 who have substantial neuroinflammation, and who are therefore potentially at a higher risk of developing secondary tauopathy, is unknown. It is also important to note that no direct causal link between COVID-19 and neurological or psychiatric sequelae has been found, and some complications—including anxiety disorders—might be due to the stress and trauma associated with social factors (eg, isolation) and treatment options (eg, intubation).[1]

We believe that follow-up studies of neurological dysfunction in survivors of COVID-19 should be done, particularly in people who showed acute or subacute neurological symptoms. Such studies should persist for at least a decade and focus on young individuals (ie, those aged 30–40 years), to reduce the proportion of participants who will develop tauopathies because of old age. These studies should also investigate tau in blood or CSF, and tau aggregation by use of PET tracers.

RP reports being a co-founder and consultant for Faze Medicines. JP and EL declare no competing interests.

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